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Gene for Anhidrotic Ectodermal Dysplasia Identified

The discovery of the EDA gene resulted from the international collaborative effort of universities, private foundations, and government. Representing these groups are, from left: Dr. Jonathan Zonana, Oregon Health Sciences University; Dr. Juha Kere, University of Helsinki; Ms. Mary Kaye Richter, National Foundation for Ectodermal Dysplasia; and Dr. Harold Slavkin, Director, National Institute of Dental Research.

In 1875, Charles Darwin described a peculiar disorder that appeared in each generation of one family's male members, affecting some, sparing others. The mysterious condition became apparent in the very young, manifesting itself with "...small and weak incisor teeth...very little hair on the body...excessive dryness of the skin..." In addition to the obvious symptoms, Darwin also noted that "Though the daughters in the above family were never affected, they transmit the tendency to their sons; and no case has occurred of a son transmitting it to his sons." With a few simple observations, Darwin launched a scientific inquiry that has finally led to the discovery of the gene for anhidrotic ectodermal dysplasia (EDA).

In the early 1970s, a little less than 100 years after Darwin's description, the EDA gene became the first gene mapped to the X chromosome. It has taken roughly two more decades, but an international team of scientists, led by Dr. Juha Kere of the University of Helsinki and Dr. Anand Srivastava from the University of Washington in St. Louis, has pinpointed the location and identified the structure of the gene. This work, sponsored in part by the NIDR and the National Center for Human Genome Research, was published in the August issue of *Nature Genetics*. With this discovery, scientists have provided a molecular marker to identify female carriers of the disorder, and are a step closer to developing therapeutic interventions to prevent or alleviate symptoms in affected individuals.

Males Affected

Still, little is known about what occurs at the molecular level to ultimately produce the unique clinical features of EDA. The name itself refers to the abnormal development (dysplasia) of tissues that are derived from ectoderm, the outermost of the three primary layers of the embryo from which is derived, among other structures, the skin, hair, nails, sweat glands, and teeth. The term "anhidrotic" refers to the underdevelopment or absence of sweat glands, a condition that can be life threatening because it prevents the body from cooling down during fevers or periods of excessive heat. Other features that affect the quality of life for these young children include baldness and often the need for dentures or dental implants to compensate for the absence of teeth.

Of the more than 150 different forms of ectodermal dysplasia, mutations in the X chromosome account for about half of all cases. As was noted by Darwin, the "X-linked" form of ectodermal dysplasia is associated with male children. Males have but a single X chromosome inherited from the mother, along with a Y chromosome from the father. Females inherit an X from each parent. When a male inherits a mutated EDA gene from the mother, he has no back-up normal gene on a second X chromosome, as is the case with females. Males with

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the mutation come down with ectodermal dysplasia, females may have mild symptoms but mainly act as carriers, transmitting either a normal or mutated X chromosome to their offspring.

Females Provide Clues

Interestingly, it was two female patients with all the symptoms of X-linked EDA that led Drs. Kere, Srivastava, and colleagues to the discovery of the gene. Earlier work by NIDR grantee and co-author Jonathan Zonana had identified an unusual chromosomal rearrangement in one of the girls. The X chromosome had been sheared in two, with one piece sticking to the end of chromosome 9 and the remainder forming a truncated X. A similar X translocation was identified by other investigators in the second girl. Although the break points occurred in slightly different locations, both destroyed the function of the EDA gene, indicating that the breaks occurred within the region of the chromosome that contains the gene. In other disorders where X translocations have been identified as the cause, the normal X chromosome is inactivated, leaving no functional copy of the gene. The disorder manifests itself as it would in males.

The breakpoint information, coupled with several studies that followed the inheritance pattern of known genetic markers on the X chromosome, narrowed the position of the gene to a region known as Xq12-q13.1. Once this region had been identified, it became a painstaking task of identifying the telltale DNA sequences that are characteristic of a gene, and looking for a matching gene product in the cell types that are affected by EDA.

The investigators identified a gene within this region of the X chromosome that contains the molecular code to produce a 135-amino acid protein. This novel protein has a predicted structure compatible with a transmembrane molecule, a protein that is part of the cell membrane and falls within the category of receptors, growth factors, or adherence molecules. The protein was detected in fetal tissues and certain types of adult skin cells that are consistent with the pathology of EDA.

Mouse Studies Helpful

The function of the protein remains unknown, but some exciting hints are provided by a strain of mouse called Tabby, named for its unusual pattern of hair markings. The mice have a mutation in the X chromosome region that is the mouse equivalent of the human EDA gene location. The mice are afflicted with some of the same symptoms that appear in humans, including missing sweat glands and abnormally shaped and/or missing teeth.

When newborn mice are injected with a protein called epidermal growth factor, the developmental defects are partially reversed. The product of the Tabby gene appears to be involved in molecular signaling events that affect the development of ectodermal tissues. Future studies will determine if the mouse and human genes are comparable, and will pursue the function of the human EDA protein and the role it plays in the formation and growth of hair, sweat glands, and teeth.

The investigators participating in this international collaborative effort were Juha Kere, Outi Montonen, Sini Ezer, Albert de la Chapelle, and Ulpu Saarialho-Kere, University of Helsinki; Anand K. Srivastava and David Schlessinger, Washington University School of Medicine; Jonathan Zonana, Betsy Ferguson, and Felix Munoz, Oregon Health Sciences University; Nick Thomas, Delyth Morgan, and Angus Clarke, University of Wales College of Medicine; and Ellison Y. Chen, Advanced Center for Genetic Technology, Foster City, California.

The study was supported by grants from the Sigrid Juselius Foundation, the Academy of Finland, Finska Läkaresällskapet, the Folkhälsan Institute of Genetics, the NIDR and National Center for Human Genome Research at the National Institutes of Health, the National Foundation for Ectodermal Dysplasias, and the Wellcome Trust. ■

—Wayne Little

Dental Students Explore Research or, 'How I Spent My Summer Vacation'

'Awesome' is the term Deborah Clark-Holke uses to summarize her experience at the NIDR. "I love pounding away at a problem in the lab!" says the 25-year-old, one of 10 dental students who spent part of the summer conducting research at the NIDR. "Even though research is sometimes frustrating, it's a challenge that keeps pulling me back," she says. A student at the College of Dentistry, University of Iowa, Clark-Holke describes her participation in the NIDR Summer Dental Student Award (SDSA) program as an experience she would definitely like to repeat.

Launched this year, the SDSA program gives dental students a glimpse of research by offering them a chance to gain hands-on experience at the NIDR for 6 to 12 weeks. Clark-Holke and nine other students were chosen from 30 applicants to participate in the program. Each student was matched with a mentor and chose a research project according to their interests and experience.

"I think the program offers a unique opportunity for students to 'try out' research as a career," said program

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manager Dr. Marian Young, of NIDR's Bone Research Branch. "It's a chance for them to see how science is organized, how it works, and whether or not it's something they want to pursue."

Most of the SDSA students already had some research experience. Others hadn't, but expressed an interest in finding out what life in the lab was all about. Geoff Steinkruger, a student at the College of Dental Medicine, Medical University of South Carolina, found the summer program an excellent opportunity "to see another side of science." During his eight weeks at the NIDR, he worked in the Laboratory of Cellular and Developmental Oncology studying the cell signal protein Transforming Growth Factor-Beta. "It's really been an eye-opening experience for me," said the 24-year-old, who had his first brush with research in the summer program. "I am amazed at the diversity of research both at NIDR and NIH."

Although many of the students had worked in a lab, to some, the thought of working at NIH seemed a bit intimidating at first. But the overwhelming feeling among the students was one of eagerness to get here and "do science."

"I have wanted to do research ever since I was a sophomore in college," said Kapil Vij, 24, who attends the College of Dentistry, University of Illinois at Chicago. "I was anxious to get here and get going on my own projects right from the start." Working with scientists in NIDR's Neurobiology and Anesthesiology Branch, Vij completed two studies on the opiate-like peptide dynorphin in rats.

"What better place is there to do science?" said Mark Berkman, who enthusiastically accepted the opportunity to spend his summer on the NIH campus. The student from the Ohio State University College of Dentistry searched the MEDLINE database to find out which NIDR mentor had done work in embryology, a topic of great interest to him. He found NIDR director Dr. Harold Slavkin. "When I came across Dr. Slavkin's work on cartilage development, I knew that I wanted to work in his lab," said the 21-year-old, who spent nine weeks studying chondrogenesis, or cartilage formation.

Pictured with NIDR Director Harold Slavkin (seated far left), NIDR intramural director Henning Birkedal-Hansen (standing, third from left) and SDSA program manager Dr. Marian Young of the NIDR Bone Research Branch (standing, fourth from right), are some of the students who participated in the 1996 NIDR Summer Dental Student Award program.

"Is Research Really For Me?"

Between their time in the lab, the informal get-togethers, and the more structured activities like tours and presentations, the students were treated to a panel discussion that featured dentists who had pursued research careers. Sponsored by Dr. Henning Birkedal-Hansen, director of NIDR's Division of Intramural Research, the informal seminar was a chance for students to "ask the experts" frank questions about careers in research.

Panel members spoke of their experiences in combining clinical work with research, and answered questions that ranged from, 'do you ever have days when you feel research isn't for you?'—which drew laughter from the panel members—to 'how do I choose a Ph.D. subject area?', and, more basically, 'how do I know if research is really for me?'

"Get involved with research while you're in school," advised panelist Dr. Richard Ranney, dean of the Baltimore College of Dental Surgery, University of Maryland. "You need to look within your university—the dental school as well as the medical school—and talk to the people doing research." Other panel members echoed the "get involved" philosophy and many also suggested that students find a mentor who could offer them guidance.

As the summer wound down, the students departed for their schools and another year of academic pursuits. "I think it was a productive summer for them," said Young. "The reaction I heard was, 'wow—so this is research; it's really interesting!' I wouldn't be surprised if many of them choose it as a career."

"I met some high caliber people at NIDR and have learned a great deal," said Clark-Holke, who described her seven weeks at the institute as "too short."

Adds Berkman, "I was engrossed in science and engrossed in learning . . .

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It was an absolutely fantastic way to spend my summer."

Kapil Vij, who will make a presentation on the program to incoming students when he returns to school, says he hopes NIDR continues and expands the program. "This summer's experience was like a teaser," he said. "I would like to come back."

Additional Information

For further information about the program and application dates for the 1997 SDSA awards, contact:

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—*Mary Daum*

NEW RFAs ISSUED

The NIDR Division of Extramural Research has issued two new Requests for Applications (RFAs):

Developmental Grants: Comprehensive Oral Research Centers

This RFA is for developmental grants to support the planning of multidisciplinary Comprehensive Oral Health Research Centers of Discovery (RCD).

The aim of the RCD program is to support a full range of multidisciplinary research on oral, dental, and craniofacial diseases and disorders. The RCDs will be organized around a central theme that falls within the mission of the NIDR. Five organizational elements will be required: (1) a biomedical, behavioral, social science and health services research base, (2) a demonstration research component that provides a means for developing effective outreach and community liaison functions, (3) a component for research concerning education of health professionals and future scientists, (4) a technology transfer component that supports developmental activities to move fundamental and clinical research findings from the laboratory to the marketplace, and (5) administration and research support cores appropriate to the focus of the research. The RCDs may consist of newly proposed components or incorporate already existing research projects, program projects, or research centers into a proposed center.

The one-year planning grant available through this RFA is expected to lead to the development of an organizational infrastructure necessary for the establishment of an RCD and the eventual submission of an application to support its activities. Applications for planning grants may be submitted by public and private organizations including universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the Federal government. The RFA will use the Developmental Grant (P20) mechanism. Depending on the scientific merit of applications received, NIDR expects to fund 10-15 planning grants.

The application receipt date is November 14, 1996; the anticipated award date is July 1997.

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Collaborative Opportunities for Research on Minority Oral Health (CORMOH)

Through the CORMOH program, NIDR is seeking applications for research grants from investigators at minority institutions to support collaborative biomedical and behavioral research between scientists at minority institutions and investigators at research-intensive institutions. The purpose of this RFA is to increase the racial and ethnic diversity of the pool of scientists contributing to oral and craniofacial health research. It also aims to enhance the capacity to conduct meritorious research at minority institutions, and to support basic and clinical research relevant to improving the oral and craniofacial health status of U.S. racial and ethnic minority populations.

Applications in response to this RFA may be submitted from investigators at domestic, public or private minority institutions such as dental or medical schools, research institutions, and universities. To be eligible, the principal investigator must be a member of a U.S. racial or ethnic minority, an employee of a minority institution, and propose an affiliation with an investigator at one or more research-intensive institutions.

NIDR plans to make up to 10 awards if sufficient applications of high scientific merit are received. The application receipt date is June 20, 1997; the anticipated award date is June 1998.

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The *NIDR Research Digest* is published periodically by the National Institute of Dental Research. Its purpose is to communicate NIDR research findings and other activities of interest to those working in the field of dental research.

Requests for additional information on NIDR or its programs may be addressed to: NIDR, Public Information and Reports Branch, 31 Center Drive MSC 2290 Bethesda, MD 20892-2290. Telephone (301) 496-4261.